

**EXHIBIT-I**

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

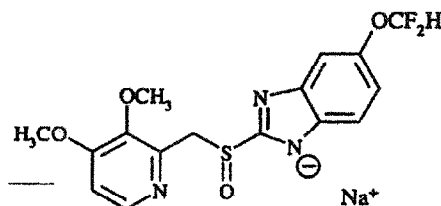
*APPLICATION NUMBER:*  
**20988**

**DRAFT FINAL PRINTED LABELING**

**PROTONIX® I.V.**  
(pantoprazole sodium)  
for Injection

**DESCRIPTION**

The active ingredient in PROTONIX® I.V. (pantoprazole sodium) for Injection is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is  $C_{16}H_{14}F_2N_3NaO_4S$ , with a molecular weight of 405.4. The structural formula is:



Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. The reconstituted solution of PROTONIX I.V. for Injection is in the pH range 9.0 to 10.0.

PROTONIX I.V. for Injection is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing pantoprazole sodium, equivalent to 40 mg of pantoprazole.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Pantoprazole peak serum concentration ( $C_{max}$ ) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following the administration of PROTONIX I.V. for Injection, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see **CLINICAL PHARMACOLOGY, Metabolism**) with normal liver function receiving a 40 mg dose of PROTONIX I.V. for Injection by constant rate over 15 minutes, the peak concentration ( $C_{max}$ ) is 5.52  $\mu\text{g/mL}$  and the total area under the plasma concentration versus time curve (AUC) is 5.4  $\mu\text{g}\cdot\text{hr/mL}$ . The total clearance is 7.6-14.0 L/h and the apparent volume of distribution is 11.0-23.6 L.

***Distribution***

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

***Metabolism***

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10.0 hours, they still have minimal accumulation ( $\leq 23\%$ ) with once daily dosing.

***Elimination***

After administration of a single intravenous dose of  $^{14}\text{C}$ -labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

***Special Populations******Geriatric***

After repeated I.V. administration in elderly subjects (65 to 76 years of age), pantoprazole AUC and elimination half-life values were similar to those observed in younger subjects. No dosage adjustment is recommended based on age.

***Pediatric***

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

***Gender***

After oral administration there is a modest increase in pantoprazole AUC and  $C_{\text{max}}$  in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is warranted based on gender (Also see Use in Women).

***Renal Impairment***

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

### **Hepatic Impairment**

Oral administration studies (absolute bioavailability is approximately 70%) were performed in patients with mild to moderate hepatic impairment. Maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum elimination half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in drug accumulation following once daily multiple-dose administration equal to or less than 21%. No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Caution should be exercised when administering PROTONIX® I.V. for Injection in patients with hepatic impairment.

### **Drug-Drug Interactions**

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

### **Pharmacodynamics**

#### **Mechanism of Action**

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H<sup>+</sup>, K<sup>+</sup>)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related up to a daily dose of 80 mg and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H<sup>+</sup>, K<sup>+</sup>)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

#### ***Antisecretory Activity***

The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single doses (20 to 120 mg) of PROTONIX I.V. for Injection were assessed in a single-dose, open-label, placebo-controlled, dose-response study. Healthy subjects received a continuous infusion for 25 hours of pentagastrin (PG) at 1  $\mu\text{g/kg/h}$ , a dose known to produce submaximal gastric acid secretion. The placebo group showed a sustained, continuous acid output for 25 hours, validating the reliability of the testing model. PROTONIX I.V. for Injection had an onset of antisecretory activity within 15 to 30 minutes of administration. Doses of 20 to 80 mg of PROTONIX I.V. for Injection substantially reduced the 24-hour cumulative PSAO in a dose-dependent manner, despite a short plasma elimination half-life. Complete suppression of PSAO was achieved with 80 mg within approximately 2 hours and no further significant suppression was seen with 120 mg. The duration of action of PROTONIX I.V. for Injection was 24 hours.

In one study of gastric pH, pantoprazole was administered orally (40 mg enteric coated tablets) or intravenously (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was median percent of time that pH was  $\geq 4$  and the results were similar for intravenous and oral medications; however, the clinical significance of this parameter is unknown.

#### ***Serum Gastrin Effects***

Serum gastrin concentrations were assessed in a placebo-controlled five-day study of intravenous pantoprazole with 40 and 60 mg doses. Following the last dose on day 5, the median 24-hour serum gastrin concentrations were elevated by 3-4 fold compared to placebo in both 40 and 60 mg dose groups. However, by 24 hours following the last dose median serum gastrin concentrations for both groups returned to normal levels.

#### ***Enterochromaffin-Like (ECL) Cell Effects***

There are no data available on the effects of intravenous pantoprazole on ECL cells.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility).

### Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

### Clinical Studies

A multicenter, double-blind, two-period placebo-controlled study was conducted to assess the ability of PROTONIX I.V. for Injection to maintain gastric acid suppression in patients switched from the oral dosage form of pantoprazole to the intravenous dosage form. Gastroesophageal reflux disease (GERD) patients (n=65) with a history of erosive esophagitis were randomized to receive either 20 or 40 mg of oral pantoprazole once per day for 10 days (period 1) and, then were switched in period 2 to either daily intravenous pantoprazole or placebo for 7 days, matching their respective dose level from period 1. Patients were administered all test medication with a light meal. Maximum acid output (MAO) and basal acid output (BAO) were determined 24 hours following the last day of oral medication (day 10), the first day (day 1) of intravenous administration and the last day of intravenous administration (day 7). MAO was estimated from a 1 hour continuous collection of gastric contents following subcutaneous injection of 6.0 µg/kg of pentagastrin.

This study demonstrated that, after 10 days of repeated oral administration followed by 7 days of intravenous administration, the oral and intravenous dosage forms of PROTONIX 40 mg are similar in their ability to suppress MAO and BAO in patients with GERD (See table below). Also, patients on oral PROTONIX who were switched to intravenous placebo experienced a significant increase in acid output within 48 hours of their last oral dose. However, at 48 hours after their last oral dose, patients treated with PROTONIX I.V. for Injection had a significantly lower mean basal acid output than those treated with placebo.

ANTISECRETORY EFFECTS (mEq/h) OF 40 mg PROTONIX I.V. for INJECTION  
AND 40 mg ORAL PROTONIX IN GERD PATIENTS

Parameter	PROTONIX Delayed-Release Tablets DAY 10	PROTONIX I.V. for Injection DAY 7	Placebo I.V. DAY 7
Mean maximum acid output	6.49 n=30	6.62 n=23	29.19* n=7
Mean basal acid output	0.80 n=30	0.53 n=23	4.14* n=7

\*P < 0.0001 Significantly different from PROTONIX I.V. for Injection.

Data comparing PROTONIX I.V. for Injection to other proton pump inhibitors (oral or I.V.) or H2 receptor antagonists (oral or I.V.) are limited, and therefore, are inadequate to support any conclusions regarding comparative efficacy.

**INDICATIONS AND USAGE**

PROTONIX I.V. for Injection is indicated for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative to oral therapy in patients who are unable to continue taking PROTONIX (pantoprazole sodium) Delayed-Release Tablets. Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

**CONTRAINDICATIONS**

PROTONIX I.V. for Injection is contraindicated in patients with known hypersensitivity to the formulation.

**PRECAUTIONS****General**

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (<21%), when dosed as recommended at 40 mg once daily, needs to be weighed against the potential for reduced acid control when decreasing the dose or altering the dosing regimen in these patients.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets.

**Drug Interactions** (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**)

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month oral toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to

50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

#### **Pregnancy**

##### ***Teratogenic Effects***

##### ***Pregnancy Category B***

Teratology studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### **Nursing Mothers**

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

#### **Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Use in Women**

No gender-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 166 men and 120 women with GERD. Erosive esophagitis healing rates in the 221 women treated with oral pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

**Use in Elderly**

No age-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 86 elderly ( $\geq 65$  years old) and 200 younger ( $< 65$  years old) patients with GERD. Erosive esophagitis healing rates in the 107 elderly patients ( $\geq 65$  years old) treated with oral pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of oral pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

**ADVERSE REACTIONS****Safety Experience with Intravenous Pantoprazole**

Intravenous pantoprazole has been well tolerated in clinical trials of GERD patients and healthy subjects. A double-blind placebo controlled study conducted in the U.S. evaluated the effect of PROTONIX I.V. for Injection on pentagastrin-stimulated acid secretion in 65 GERD patients. Treatment-emergent events considered possibly, probably or definitely drug-related that were reported by 2 or more patients ( $\geq 4\%$ ) taking PROTONIX I.V. for Injection ( $n=50$ ) and by 0% of patients taking placebo ( $n=15$ ) were: abdominal pain (12%), chest pain (6%), rash (6%), and pruritus (4%).

Additional adverse experiences occurring in  $> 1\%$  of GERD patients treated with intravenous pantoprazole ( $n = 412$ ) in domestic ( $n = 50$ ) or international ( $n = 362$ ) clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

**BODY AS A WHOLE:** headache, injection site reaction.

**DIGESTIVE SYSTEM:** dyspepsia, nausea, diarrhea, vomiting.

**NERVOUS SYSTEM:** dizziness.

**RESPIRATORY SYSTEM:** rhinitis.

The safety of intravenous pantoprazole has also been evaluated during international clinical trials conducted in over 300 critically ill patients. The safety profile of intravenous pantoprazole was similar to that of oral pantoprazole with the exception of injection site reactions including injection site inflammation, thrombophlebitis, hemorrhage, and abscess. Head-to-head comparative studies between PROTONIX I.V. for Injection and oral PROTONIX, other proton pump inhibitors (oral or I.V.), or H2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

**Safety Experience with Oral Pantoprazole**

In short-term clinical trials in GERD patients treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of  $\geq 1\%$ .

**BODY AS A WHOLE:** headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain.

**CARDIOVASCULAR SYSTEM:** migraine.

**DIGESTIVE SYSTEM:** diarrhea, flatulence, abdominal pain, cructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

**HEPATO-BILIARY SYSTEM:** liver function tests abnormal, SGPT increased.

**METABOLIC AND NUTRITIONAL:** hyperglycemia, hyperlipemia.

**MUSCULOSKELETAL SYSTEM:** arthralgia.

**NERVOUS SYSTEM:** insomnia, anxiety, dizziness, hypertonia.

**RESPIRATORY SYSTEM:** bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

**SKIN AND APPENDAGES:** rash.

**UROGENITAL SYSTEM:** urinary frequency, and urinary tract infection.

Additional adverse experiences occurring in  $<1\%$  of GERD patients receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

**BODY AS A WHOLE:** abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

**CARDIOVASCULAR SYSTEM:** angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

**DIGESTIVE SYSTEM:** anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

**ENDOCRINE SYSTEM:** diabetes mellitus, glycosuria, goiter.

**HEPATO-BILIARY SYSTEM:** biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

**HEMIC AND LYMPHATIC SYSTEM:** anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

**METABOLIC AND NUTRITIONAL:** dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

**MUSCULOSKELETAL SYSTEM:** arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

**NERVOUS SYSTEM:** abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

**RESPIRATORY SYSTEM:** asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

**SKIN AND APPENDAGES:** acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

**SPECIAL SENSES:** abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

**UROGENITAL SYSTEM:** albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

#### **Postmarketing Reports**

There have been spontaneous reports of adverse events with postmarketing use of intravenous or oral pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; and pancreatitis.

In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

#### **Laboratory Values**

In US and international GERD clinical trials, the overall percentages of transaminase elevations

did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two US controlled trials of oral pantoprazole in patients with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

#### OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of oral pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

#### DOSAGE AND ADMINISTRATION

##### Treatment of Erosive Esophagitis

The recommended adult dose, as an alternative to continued oral therapy, is 40-mg pantoprazole given once daily by intravenous infusion for 7 to 10 days.

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted (admixed) with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution need to be protected from light.

PROTONIX I.V. for Injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 3 mg/min (7 mL/min). PROTONIX I.V. for Injection admixtures should be administered intravenously through a dedicated line, using the in-line filter provided. The filter must be used to remove the precipitates that may form when the reconstituted drug product is mixed with I.V. solutions. Studies have shown that filtration does not alter the amount of drug that is available for administration. If administration through a Y-site is

desirable, the in-line filter must be positioned below the Y-site that is closest to the patient. The intravenous line should be flushed before and after administration of PROTONIX I.V. for Injection with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP. PROTONIX I.V. for Injection should not be simultaneously administered through the same line with other intravenous solutions.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets. Safety and efficacy of PROTONIX I.V. for Injection as a treatment for GERD for more than 10 days have not been demonstrated (see INDICATIONS AND USAGE).

Parenteral routes of administration other than intravenous are not recommended.

No dosage adjustment is necessary in patients with mild, moderate or severe renal insufficiency or in elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis. No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Caution should be exercised when administering PROTONIX® I.V. for Injection in patients with hepatic impairment.

#### HOW SUPPLIED

PROTONIX I.V. for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial.

PROTONIX I.V. for Injection is available as follows:

NDC 0008-0923-03 One carton containing 25 vials of PROTONIX I.V. for Injection (each vial containing 40-mg pantoprazole) and 25 required in-line filters (1.2 µm pore size).

#### Storage

Store PROTONIX I.V. for Injection vials at 2°C - 8°C (36°F - 46°F) and protect from light.

Caution: the reconstituted product should not be frozen.

Store the provided in-line filters at room temperature.

Rx only

US Patent No. 4,758,579

Manufactured for Wyeth Laboratories  
A Wyeth-Ayerst Company  
Philadelphia, PA 19101  
under license from  
Byk Gulden Pharmaceuticals  
D78467 Konstanz, Germany

---

/s/

-----  
Lilia Talarico

( 3/22/01 02:50:34 PM